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TITLE: Neural Markers and Rehabilitation of Executive Functioning in Veterans with TBI and PTSD

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14. ABSTRACT The current proposal aims to explore the relationship between brain function and connectivity in selective pathways/circuits, neuropsychological functioning, and cognitive rehabilitation response in Veterans with both Traumatic Brain Injury (TBI) and Posttraumatic Stress Disorder (PTSD). Toward this end, we propose a randomized clinical trial involving a cognitive rehabilitation intervention that targets improved executive functioning, with the participation of N=100 Veterans diagnosed with both TBI and PTSD (n=50 experimental/n=50 control). We have just begun recruitment three months ago and enrolled n=64 dyads of veterans and family members at this point.				
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INTRODUCTION:

The current proposal aims to explore the relationship between brain function and connectivity in selective pathways/circuits, neuropsychological functioning, and cognitive rehabilitation response in Veterans with both Traumatic Brain Injury (TBI) and Posttraumatic Stress Disorder (PTSD). Toward this end, we propose a randomized clinical trial involving a cognitive rehabilitation intervention that targets improved executive functioning, with the participation of N=100 Veterans diagnosed with both TBI and PTSD (n=50 experimental/n=50 control).

BODY:

Task 1. Prepare for Clinical Trial (months 1-9):

1a. Submit to UNC IRB (months 1-2). We will submit a complete institutional review board (IRB) application to UNC immediately upon learning about the funding decision, so that we can rapidly get approval and submit to U.S. Army Medical Research and Materiel Command (USAMRMC) for their approval.

- UNC IRB approval was obtained at month 2.

1b. Submit to USAMRMC (months 2-9). We will submit a UNC approved IRB application, informed consent forms, data collection instruments, recruitment scripts, and all other required documentation to USAMRMC prior to implementation of the study.

- USAMRMC approval was obtained at month 4.

1c. Develop Data Collection System (months 1-9). While awaiting approval from UNC IRB and USAMRMC, we will adapt our existing Microsoft Access data collection programs to the needs of the current Department of Defense (DOD) application. We will capitalize on the infrastructure of both the UNC Veterans Post-Deployment Adjustment Study and the UNC Biostatistics Core to ensure both high quality data collection and easy interface for Veterans and family members to provide the data in Microsoft Access.

- The data collection system was created and completed at month 9. The database is fully functional and permits research coordinators to add information from clinical interviews and cognitive testing and Veterans to add self-report data.

1d. Train Research Assistants to Facilitate Cognitive Rehabilitation (months 6-9). The Clinical Facilitator and Drs. Elbogen and Johnson will assure that research assistants are trained to a high level of fidelity to implement the components of the cognitive rehabilitation intervention. Research assistants will complete training and achieve at least 90% on the intervention fidelity checklist, as described in the clinical protocol.

- We hired research assistants and coordinators by month 6.
- Research assistants' baseline interviews/testing, interventions, and follow-up interviews/testing were observed for fidelity by month 8.
- After three sessions observed of each, all research assistants achieved 90% of fidelity criteria using a fidelity checklist by month 12.

- Research assistants can now proceed with data collection and interventions unsupervised. Data collection and interventions are being supervised quarterly to prevent drift from the protocol.

1e. Arrange Transportation between Lab and UNC Hospital (months 6-9). To reduce participant burden, Veterans and family members will be able to park free at Dr. Elbogen's laboratory conveniently located at Carolina Crossing within 1/10 of a mile of the interstate. To further reduce participant burden, we will transport Veterans five minutes away to the Dr. Belger's lab at UNC Hospital where EEG and fMRI will be conducted and then transport Veterans back to our laboratory. We will assure transportation is running efficiently and without delays before study commencement.

- Transportation to the EEG and fMRI was arranged through the UNC-Chapel Hill School of Medicine at month 9. Participants may either take a shuttle from the research laboratory to the UNC Hospital complex, or they will be given a free parking pass.

Task 2. Baseline Interview/Data Collection (months 9-36):

2a. Recruitment (months 9-36). As outlined in project narrative and letters confirming access to military populations, we will recruit Veterans with TBI and PTSD from Dr. Elbogen's National Institute of Mental Health (NIMH) study, the Durham VA Trauma Research database, the VA Mid-Atlantic Health Care Network (VISN6) Mental Illness Research Education and Clinical Centers (MIRECC) Registry, and UNC Hospitals to meet our targeted recruitment. We will call Veterans and family members from these sources using IRB-approved protocols and phone scripts.

- We have been actively recruiting from the Durham VA and UNC since month 10. We have contacted Veterans through research registries at the Durham VA, and we have hung flyers with study information at the Durham VA and UNC Hospitals.
- We have also added recruitment from Veteran and Brain Injury organizations throughout North Carolina in month 10.
- We have presented our study at the North Carolina Veteran Service Organization annual conference in month 11.
- We participated in a Military and Veterans Networking Fair in Raleigh, NC in month 12.
- We created a Facebook Page at UNC to further advertise for the study in month 14.
- We started recruitment through local universities and community colleges in month 17. We have had notable success at Fayetteville Community College, located near Fort Bragg Army Base.

Targeted Recruitment: By end of year one, we aim to have enrolled N=10 participants. By end of year two, we aim to have enrolled N=50 participants. By end of year three, we aim to have enrolled N=85 participants.

- Our recruitment is going well. At month 24 we have enrolled n=65 Veteran-family dyads. We have a total of n=5 scheduled through December 2013. At the current rate, we will continue to exceed short targets for recruitment and should meet long term overall targeted recruitment.

2b. Informed Consent (months 9-36). The nature and the purpose of the research, the study procedures, standard protections for human subjects, and risks and benefits of the study will be

explained to Veterans and family members. If both the Veteran and a family member consent, they will sign informed consent documents.

- Informed consent for both Veterans and family members has occurred for the past fifteen months. Participants have understood the protocol and no issues have arisen.
- Research assistants carefully explain the informed consent information to the Veteran dyads and make it clear that participation is voluntary.

2c. Initial Screening (months 9-36). We will ensure that Veterans meet study criteria for PTSD and TBI and ensure that Veterans are safe for EEG and fMRI procedures. We will also assess whether Veterans and/or family members have difficulties with decisional capacity that may impair their ability to provide informed consent.

- We have been conducting initial screening with success and have had few problems to report.
- Research assistants carefully use TBI and PTSD screening measures to ensure that Veterans meet study criteria.

2d. Interview (months 9-36). After the EEG and fMRI, Veterans will be transported back to Dr. Elbogen's lab. Depending on the time and how Veterans and family members feel, the interview portion of the data collection, which lasts 60 to 90 minutes, may be conducted the same day, or it may be rescheduled within a week if Veterans and/or family members are feeling tired at that point in time. Please note that data is entered directly by participants and research staff into Microsoft Access; thus, there is no need for data entry or double scoring on this study.

- To prevent the Veterans from becoming overtired, we have found that it works best to schedule the interview and testing in the research lab in the same week but on a different day than the MRI and EEG.
- In total, we have completed n=65 baseline interviews of veteran/family dyads by month 24.

2e. EEG/fMRI (months 9-36). The details for these procedures are provided in the project narrative. Briefly, after the initial screening confirms that Veterans meet study criteria, Veterans will be transported to UNC Hospital for EEG and fMRI procedures, which should take four to five hours

By month 24, we have had 53 participants successfully completed baseline MRIs and 59 successfully complete baseline EEGs.

Task 3. Implementation of Clinical Trial (months 9-42):

3a. Randomization Procedure (months 9-36). Following successful completion of the informed consent process and the baseline interview, the research coordinator will randomly assign Veterans to study conditions using a computerized procedure available to tracking systems using Microsoft Access.

- Participants are randomly assigned to study conditions by the clinical coordinator, using the Microsoft Excel RAND feature. Research assistants remain blind to participant assignment until after the baseline interview and cognitive testing have been completed. Research assistants are informed of the participant group assignment for only those veterans with whom they will be conducting individual support sessions.

3b. Initiating Intervention (months 9-36). Depending on the time and how Veterans and family members feel, initiation of the intervention may be conducted the same day as data collection, which lasts 30 to 45 minutes, or may be rescheduled within a week if Veterans and/or family members are feeling tired at that point in time. All participants will receive an iPod Touch with instructions for applications to complete as part of the study, and they will be taught how to log application use on the iPod.

- To date, 54 Veteran-family dyads have successfully completed baseline individual support sessions. 25 were randomized to the experimental arm and 29 were randomized to the control arm.
- No technical difficulties concerning the iPod Touch have been reported.

3c. Experimental Group - (months 9-42). Veterans in the experimental group will be complete cognitive rehabilitation interventions that have shown empirical support in the research literature to improve executive functioning. Training for Goal Management Training lasts 45 to 60 minutes and involves both the Veteran and family member. Components of this intervention will be administered via the iPod touch, including the n-Back procedure.

- 25 baseline in-home support sessions have been conducted with participants assigned to the experimental group.
- Research assistants were observed during the first three in-home support sessions for fidelity to intervention protocols and achieved 90% fidelity.
- Ongoing random fidelity checks are being conducted at least once quarterly.

3d. Control Group (months 9-42). Veterans in the control group will also receive an iPod touch where they will be asked to practice applications that involve motor skills as well as basic memory skills.

- 29 baseline in-home visits have been conducted with participants in the control group.
- As with the experimental group, research assistants were observed during the first three in-home support sessions for fidelity to control protocols and achieved 90% fidelity.
- Ongoing random fidelity checks are being conducted at least once quarterly.

3e. Individualized Support Sessions (months 9-40). At two months and four months, a trained facilitator will visit Veterans in their homes or place of convenience in order to collect data from iPod logs, make behavioral observations, and review intervention protocols.

- By month 24, a total of 40 two-month in-home support sessions were completed. There were no problems with implementation.
- By month 24, a total of 23 four-month in-home support sessions were completed. There were no problems with implementation.

Task 4. Follow-up Interview/Data Collection (months 9-42):

4a. EEG/fMRI (timeframe, e.g., months 9-42). The details for these procedures are provided in the project narrative. Veterans will park conveniently at Carolina Crossing B and be transported to UNC Hospital for EEG and fMRI procedures, which should take about four to five hours.

- 23 Follow-up EEG sessions have been completed and 18 follow-up MRIs have been completed.

4b. Interview (timeframe, e.g., months 9-42). After the EEG and fMRI, Veterans will be transported back to Dr. Elbogen's lab at Carolina Crossing. Depending on the time and how

Veterans and family members feel, the interview portion of the data collection, which lasts 60 to 90 minutes, may be conducted the same day or may be conducted within a week if Veterans and/or family members are feeling tired at that point in time.

- 25 six month interviews of veteran-family dyads have been completed.

Summary of Recruitment Numbers (as of 10/25/13):

Enrollment

Number of Both Veterans and Collateral Signed Consents:	65
Scheduled (for appointment in November)	6
Currently Enrolled on the study (between 0-6 months)	32
Completed (6 month assessment)	25
Lost to Follow up	4
Withdrawn (dropped out after baseline)	8

Home Visits

0 Month Control Home Visit	29
0 Month Experimental Home Visit	25
2 Month Control Home Visit	22
2 Month Experimental Home Visit	18
4 Month Control Home Visit	13
4 Month Experimental Home Visit	10

Neuroimaging

MRI @ Baseline	54
EEG @ Baseline	60
MRI @ Follow-up	18
EEG @ Follow-up	23

Task 5. Data Analysis and Deliverables (months 9-48)

5a. Quality Assurance (months 9-48). Throughout the data collection procedures, the research coordinator will randomly select 20% of participants and conduct an audit of Microsoft Access data and informed consent documents every six months of the project.

- MRIs have been examined for quality assurance methodologies described in Lee Friedman and Gary H. Glover (2006) Report on a Multicenter fMRI Quality Assurance Protocol, Journal of MRI, 23:827–839. MRI protocols showed very little participant physical movement during scanning and demonstrated MRI data was clear and could be analyzed according to the current application's protocol.
- 52 consent forms were randomly selected to determine if research assistants were completing these as per protocol. There were a few minor typos but otherwise no major problems detected.
- 82% of veteran participants' interviews and 28% of collateral participants' interviews were randomly selected to determine if data was entered accurately into Microsoft Access. We had 99% accuracy in data entry. Any minor entry errors were immediately corrected.

5b. Data Analysis (months 40-48). Statistical analytics procedures, as outlined in the application, will be conducted once baseline and follow-up data are collected.

- We have started to examine cross-sectional baseline data on fMRI, EEG, and neuropsychological functioning with respect to executive dysfunction and disinhibition in veterans with TBI and PTSD.
- We have also been analyzing relevant data on TBI, frontal dysfunction, and criminal behavior in a national dataset of TBI.

5c. Conference Presentations (months 12-48). Throughout the course of the grant, we will present progress on the grant at national scholarly meetings.

- Not applicable at this time.

5d. Manuscript Preparation (months 42-48). Once data is analyzed, we will prepare scientific manuscripts and submit to peer-reviewed journals.

- We have completed analyses relevant data on TBI, frontal dysfunction, and criminal behavior in a national dataset of TBI and are currently preparing a manuscript, slated to be ready for submission by January 2014.

5e. Research Brief (months 44-48). We will summarize the projects in a brief to be sent to each military branch, as well as to VA Centers, including Centers of Excellence, MIRECC, VA Health Services and Development Centers and VA Quality Enhancement Research Initiative Centers.

- Not applicable at this time.

KEY RESEARCH ACCOMPLISHMENTS: Bulleted list of key research accomplishments emanating from this research.

- We have no research accomplishments at this time. We are glad to report, though, that we exceeded our targeted enrollment for year 2.

REPORTABLE OUTCOMES: Provide a list of reportable outcomes that have resulted from this research to include:

- We have no reportable outcomes thus far as data collection is continuing and the randomized clinical trial is still in process.

CONCLUSION: Summarize the results to include the importance and/or implications of the completed research and when necessary, recommend changes on future work to better address the problem. A "so what section" which evaluates the knowledge as a scientific or medical product shall also be included in the conclusion of the report.

It is estimated that up to half of all military service members with combat-related traumatic brain injury (TBI) also meet criteria for Posttraumatic Stress Disorder (PTSD). TBI and PTSD are both characterized by deficits in multiple cognitive domains, including attention, executive function, and affective and cognitive control. However, cognitive and affective sequelae associated with TBI are compounded by the presence of PTSD symptoms in returning Veterans. Specifically, it has been shown that significant frontal lobe dysfunction, particularly disinhibition, occurs more often among Veterans with both TBI and PTSD than among Veterans diagnosed with only one of these conditions. The combination of TBI and PTSD in Veterans has also been linked to problems with anger and violence, which are common complaints of Veterans seeking mental health services post-deployment and have been shown to predict poor treatment outcomes in Iraq and Afghanistan Veterans. Executive dysfunction, especially

difficulty with attentional processing, is strongly related to hostility and aggressiveness in Iraq and Afghanistan Veterans; increasingly so in the presence of TBI and PTSD.

Understanding the neurobiology and neuropsychology associated with an evidence-based cognitive rehabilitation intervention will allow us to identify Veterans with both TBI and PTSD who are predisposed to positive treatment outcomes. To our knowledge, this will be the first attempt to integrate neurobiological and neurocognitive techniques with information about the efficacy of a theoretically and empirically driven cognitive rehabilitation intervention in Veterans with combined TBI/PTSD diagnoses. Additionally, this research may suggest additional avenues for assessment of clinical intervention efficacy and the identification of therapeutic targets (e.g. alteration of function in fronto-limbic circuits) relevant to the military population. Future studies could investigate whether adjunctive treatment with antianxietyolitic agents, such as oxytocin, may have additional implications for effective cognitive rehabilitation of Veterans with both TBI and PTSD, by either increasing efficacy in the responders or facilitating processing along fronto-limbic pathways critical for attention and executive function.

Our goal is to identify subgroups of individuals who are more or less likely to benefit from specific intervention strategies and thus be better able to develop individualized treatment protocols with a higher likelihood of success for the individual Veteran. Better understanding of the cognitive rehabilitation process in these TBI patients who are also suffering from PTSD will help define resources and costs of medical care necessary to adequately address many of the issues raised in this population. Given the links between TBI/PTSD, executive dysfunction, and anger, impulsivity, and aggression, efforts to rehabilitate cognitive function will be particularly important to ensure that current and future Veterans adjust successfully when they return home to their families, workplaces, and communities.

REFERENCES:

- Not applicable at this time.

APPENDICES:

- Not applicable at this time.

SUPPORTING DATA: All figures and/or tables shall include legends and be clearly marked with figure/table numbers.

- Not applicable at this time.